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WHICH INSULIN IN CATS?

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The administration of insulin is the most important part of the treatment regimen in diabetic cats and should be initiated as soon as possible after the diagnosis is established. In the last two decades, the development of insulin for human use has undergone revolutionary changes, which have had important implications in veterinary medicine. First, insulins derived from animal sources are being replaced by recombinant human preparations and will eventually disappear from the market. Although there are differences in the amino acid sequences, human insulins (and their analogues) are fortunately biologically active in cats. Second, insulin preparations for human use containing 40-IU/ml have largely been replaced by 100-IU/ml insulins. It is important that owners understand the difference, because two insulin preparations for veterinary use (Caninsulin® Vetsulin® and ProZinc®) are supplied as 40-IU/ml and using the wrong syringe size would lead to substantial dosing errors. Third, new classes of insulins called insulin analogues have been developed. They were designed to improve the pharmacodynamic properties of insulin and render insulin absorption or insulin delivery to tissues more predictable. Insulin preparations are classified as short-acting, intermediate- and long-acting and so-called premixed or biphasic insulins. Intermediate- and long-acting preparations are used for long-term control of cats with uncomplicated diabetes. The longer duration of action is achieved by slowing the rate of absorption from the subcutaneous tissue. Delayed absorption is due either to the addition of substances that are virtually inert and do not have therapeutic properties themselves (such as protamine and zinc) or to a modification of the insulin molecule (as in Lantus® and Levemir®). Levemir® has some additional protracting effect as it binds to albumin. A number of premixed or biphasic insulin formulations are available for humans to provide a more convenient approach to cover both, basal and prandial insulin requirements and consist of a mixture of a short-acting and an intermediate-/long-acting component. The use of premixed insulins has so far not been studied in cats. It is likely, however, that they will not be beneficial because cats do not have the same type of postprandial hyperglycemia as humans.

Intermediate/long-acting insulins include the following types:

Neutral Protamine Hagedorn Insulin (NPH). NPH insulin preparations are potent insulins with a marked peak. Unfortunately, duration of action is considerably less than 12 hours in most cats and their use is therefore not recommended.

Lente Insulin. A porcine-derived lente-type insulin (Vetsulin®/Caninsulin®) is licensed for use in cats in many countries and therefore often used as first-line insulin. A pen (VetPen®) allows dosing in steps of 0.5 U. Vetsulin®/Caninsulin® is a mixture of 30 – 35% short-acting amorphous and 65 – 70% long-acting crystalline insulin, in theory, this combination should result in a relatively fast onset of action and duration of action of approximately 12 hours. It should be noted, that in a substantial percentage of cats, the duration of action is quite short, and adequate control cannot be achieved.

The recently published AAHA guidelines therefore do not recommend Vetsulin®/Caninsulin® as the initial insulin option for diabetic cats.

Protamine Zinc Insulin (PZI). PZI contains more protamine than NPH and therefore has a longer duration of action. Duration of action is also longer than in lente insulin. Recently, a recombinant human PZI insulin licenced for use in cats (ProZinc®), has been released in the US, most likely, it will become available in other countries in the near future. A preliminary study showed that good glycemic control was achieved in substantial percentage of cats. In ¼ of the cats, the glucose nadir occurred later than 9 hours after administration, which may potentially lead to overlap and hypoglycemia. Clinical hypoglycemia, however, was a rare event.

Long-acting insulin analogues

Lantus® has been the focus of attention in veterinary medicine for several years because of its more constant rate of absorption and longer duration of effect compared with several other insulin preparations. Although duration of insulin glargine is quite long, BID

administration is usually required to achieve adequate control or diabetic remission. Lantus® is considered to be a peakless insulin, however, the shape of blood glucose curves vary considerably between cats and some cats reveal a pronounced peak. So far, insulin glargine has not been evaluated systematically in large clinical trials. A few pilot studies showed, that it is safe and effective in diabetic cats and adequate glycemic control can be achieved in many cases. Remission rate is assumed to be higher with Lantus® than with Vetsulin®/Caninsulin®. So far, there is little experience with Levemir®, which is another long-acting insulin analogue. Pharmacodynamic characteristics as well as remission rates seem to be similar to those of Lantus®.

Cats are unpredictable in their response to insulin and none of the insulin preparations described above are routinely effective to control the disease. We start treatment in diabetic cats with Lantus®, ProZinc® would also be a good first choice. Both insulins were recommended by the AAHA Diabetes Management Guidelines. If a diabetic cat is well regulated with Caninsulin®/Vetsulin®, there is no reason to switch to another insulin. The initial dose in cats weighing ≤ 4 kg is 1 IU/cat BID, and in cats weighing > 4 kg it is usually 1.5 IU/cat (-2.0 IU/cat) BID. In cats with an initial blood glucose concentration < 20 mmol/l, no more than 1 U/cat BID is given. The starting dose should not exceed 2.0 IU/cat BID, even in a very large cat. Very small cats (≤ 2 kg) are started on no more than 0.5 IU/cat BID. During long-term management, the most important parameters are clinical signs and blood glucose curves (BGCs). BGCs are essential for the fine-tuning of insulin dose, to detect hypoglycemia, to tailor the insulin dose in case of diabetic remission and to identify the exact problem in case of poor glycemic control. There is considerable variation in BGCs, which is more pronounced in cats with poor glycemic control. In questionable cases (discrepancy between clinical signs and BGC) another BGC should be generated after a few days before any treatment decision is taken.

The first goal is to maintain the blood glucose between 10 – 15 mmol/l and 4.5 – 7.8 mmol/l, thereafter one should consider if it is possible to achieve diabetic remission. The insulin dose should be increased in steps of 0.5 U/cat BID until the nadir is 4.5 – 7.8 mmol/l, no more often than every 5 to 7 days (except in case of hypoglycemia) as intermediate/long-acting insulin need some time to equilibrate. Lower than desired nadirs are due to insulin overdose, diabetic remission, excessive overlap of insulin actions or lack of food intake. In case the nadir is < 4.0 mmol/l the insulin dose should be reduced by 0.5 – 1.0 U/cat BID if the cat is on a low to moderate dose (0.5 – 3.0 U/cat BID) or 25 – 50% if the cat is on a higher dose. If the glucose nadir is in the desired range but duration of insulin effect is consistently less than 8 – 10 hours, the cat should be switched to an insulin preparation with longer duration of effect. Similarly, if duration of effect is longer than 14 – 16 hours, a shorter-acting insulin should be chosen.

The majority of diabetic cats needs insulin doses between 0.5 – 3.0/cat BID. If insulin dose is > 1.0 U/kg BID work-up for concurrent disease has to be considered. The decision if diabetic remission will occur or has been occurred may be challenging. In cats, in which all blood glucose concentrations of a BGC range between 4.5 and 6.7 mmol/l and serum fructosamine is < 350 μ mol/l, the insulin dose should be reduced in steps of 0.5 U/cat BID every 5 – 7 days. When a dose of 0.5 U/cat BID is reached and blood glucose is still normal, insulin administration is ceased. Thereafter, close clinical monitoring and regular glucose measurements (e.g. fasting blood glucose twice per week) is recommended.

In cases, in which generation of BGCs is not possible, insulin adjustment should be made with extreme care. The dose should be increased in small steps (0.5 U/cat BID) no more often than every 7 days until clinical signs resolve and glycosuria is reduced to trace amounts.

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